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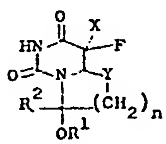
(54) **5-Fluorouracil derivatives**

(57) Novel 5-fluorouracil derivatives of the formula:



wherein R^1 is hydrogen, C_1—C_5 alkyl, C_6—C_{10} aryl, C_7—C_{10} aralkyl, C_1—C_{12} alkanoyl, C_2—C_6 alkoxycarbonyl, C_1—C_5 alkanaoyloxymethyl, carbamoyl or tri-C_1—C_5 alkylsilyl,
R^2 is hydrogen, C_1—C_5 alkyl, C_6—C_{10} aryl or C_7—C_{10} aralkyl,
X is hydrogen, halogen or C_2—C_6 alkoxycarbonyl,
Y is O, NR′ (R′ being hydrogen or C_1—C_5 alkyl); S, SO or SO_2, and
n is an integer of from 1—3,
are orally administrable anti-tumour agents.

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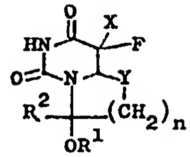
SPECIFICATION
5-fluorouracil derivatives

This invention related to novel 5-fluorouracil derivatives, which are orally administrable anti-tumour agents.

5-Fluorouracil (hereinafter abbreviated to as 5FU) has been widely used in the treatment of malignant tumours as an antimetabolic anti-tumour agent. The anti-tumour activity of 5FU is very strong, but it has many disadvantages such as the restricted scope of its application, limited dosage, forbidden continuous administration over long periods and difficult oral application because of its strong toxicity and adverse reaction of frequent occurrence. A modified 5FU derivative has been produced, FT—207 [1-(2-tetrahydrofuryl)-5-fluorouracil] [Ftorafur (Taiho Yakuhin); Jap. Pat. Unexam. Pub. Nos. 50—50383; 50—50384; 50—64281; 51—14682; 53—84981], which is a less toxic, orally and continuously administrable derivative. The activity of this compound (which is now commercially available) is, however, insufficient. Other 5FU derivatives are known and under clinical evaluation, for example, HCFU [1-n-hexycarbamoyl-5-fluorouracil] [Mitsue Seiyaku; Jap. Pat. Unexam. Pub. No. 50—148365].

The present invention provides a compound of the formula:



(I)

wherein R^1 is hydrogen, C_1—C_5 alkyl, C_6—C_{10} aryl C_7—C_{10} aralkyl, C_1—C_{12} alkanoyl, C_2—C_6 alkoxycarbonyl, C_1—C_6 alkanoyloxyymethyl, carbamoyl or tri-C_1—C_5 alkylsilyl; R^2 is hydrogen, C_1—C_5 alkyl, C_6—C_{10} aryl or C_7—C_{10} aralkyl;
X is hydrogen, halogen or C_2—C_6 alkoxycarbonyl;
Y is O, NR′ (R′ being hydrogen or C_1—C_5 alkyl), S, SO or SO_2; and
n is an integer of from 1—3.

The purpose of the present invention is to provide 5FU derivatives of the pro-drug type in order to make varied application forms possible, particularly in order to provide orally administrable derivatives having a less adverse reaction, and to improve permeability of 5FU to tumour cells. The present invention offers the compounds of the above general formula (I) as 5FU derivatives which are suitable for the above purposes.

In the above formula:—
"C_1—C_5alkyl" means straight or branched chain lower alkyl of 1—5 carbon atoms, e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or pentyl. "C_6—C_{10}Aryl" includes phenyl or naphthyl groups of 6—10 carbon atoms which may be substituted by, for example, lower alkyl (e.g. methyl, ethyl or propyl), lower alkoxy (e.g. methoxy, ethoxy or propxy), halogen (e.g. fluoro, chloro or bromo) or nitro, and examples of such groups are phenyl, p-toluyl, p-methoxyphenyl, 2,4-dimethoxyphenyl, p-chlorophenyl and p-nitrophenyl. "C_7—C_{10}Aralkyl" includes benzyl or phenethyl groups of 7—10 carbon atoms which may be substituted, including, for example, benzyl, p-methoxybenzyl, p-chlorobenzyl, p-toluyl, phenethyl and (3,5-dimethylphenyl)ethyl. "C_1—C_{12}Alkanoyl" means an alkanoic acid residue of 1—12 carbon atoms derived from a fatty acid, e.g. formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl or octanoyl. "C_2—C_6Alkoxycarbonyl" means a straight or branched chain lower alkoxycarbonyl group having 2—6 carbon atoms, e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, t-butoxycarbonyl or pentoxycarbonyl. "C_1—C_5Alkanoyloxymethyl" means an oxymethyl group substituted by an alkanoyl group of 1—5 carbon atoms, e.g. acetyloxymethyl, propionyloxymethyl, butyryloxymethyl or pivaloyloxymethyl. "Tri-C_1—C_5alkylsilyl" means a group in which the silyl is substituted by 3 C_1—C_5alkyl groups as mentioned above, e.g. trimethylsilyl, triethylsilyl, tripropylsilyl, tripentylsilyl or t-butyldimethylsilyl. "Halogen" includes chloro, bromo or iodo.

Representative compounds of the invention are:

8α-Bromo-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

8β-Fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

3α-Acetoxy-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

β-Fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

8β-Fluoro-2,3,6,7-8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine,

3α-Acetoxy-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]-pyrimidine,

8α-Bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]-pyrimidine,

8α-Bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine,

3α-(tert-Butyldimethylsilyloxy)-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

3α-(tert-Butyldimethylsilyloxy)-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

3α-(tert-Butyldimethylsilyloxy)-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]-pyrimidine,

8α-Fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

3α-Acetoxy-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

8α-Fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine,

8α-Fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine,

9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

9β-Fluoro-6,8-dioxo-4α-hydroxy-3,4,7,8,9,9aα-hexahydro-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

4α-(tert-Butyldimethylsilyloxy)-7-tert-butyldimethylsilyl-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

4α-(tert-Butyldimethylsilyloxy)-9α-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino-[3,2-c]pyrimidine,

9α-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

9α-Fluoro-3,4,7,8,9,9aα-hexahydro-4β-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

4α-Acetoxy-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

4α-Acetoxy-9α-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

4α-Acetoxy-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-octanoyloxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

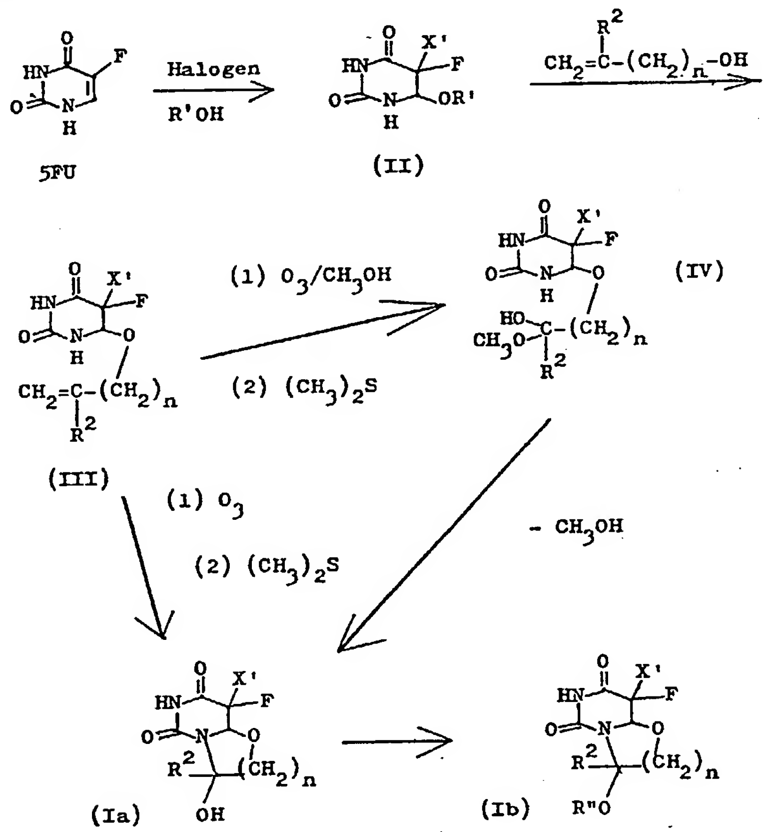
9α-Fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine,

9α-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-octanoyloxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine, and

9β-Fluoro-3,4,7,8,8,8aα-hexahydro-4α-octanoyloxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine.

The objective compounds (I) of the present invention can be produced from the known compounds according to the processes shown in the following reaction sequences.

(1) X=halogen, Y=O



In the above, R′ is hydrogen, lower alkyl or lower alkanoyl;
R″ has the same meaning as R^1 except for hydrogen; and X′ is halogen.

In the above reaction sequence, the conversion of the starting compound, 5FU, to the halogen adduct (II) may be achieved by reacting 5FU with lower alkanols or with lower alkanoic acids and the corresponding acid anhydride in the presence of a halogen (such as Br_2), the lower alkanols or alkanoic acids being represented by the general formula R′OH, according to known methods, for example, that described in J. Med. Chem. *10*, 47 (1967).

The conversion of the halogen adducts (II) to the derivatives (III) may be achieved by reaction with unsaturated alcohols represented by the general formula

$$CH_2{=}\overset{R^2}{\overset{|}{C}}{-}(CH_2)_n{-}OH$$

in the presence of a catalytic amount of acid, for example, methanesulfonic acid. The reaction may be conducted in or without a solvent with heating at the refluxing temperature for above 1—10 hours. As reaction solvents, aprotic solvents, such as, for example, benzene, toluene, acetone, acetonitrile, tetrahydrofuran, dioxane and N,N-dimethylformamide are preferably employed. In some instances the reaction may preferably be conducted in a reaction vessel equipped with a water separator containing Molecular sieves.

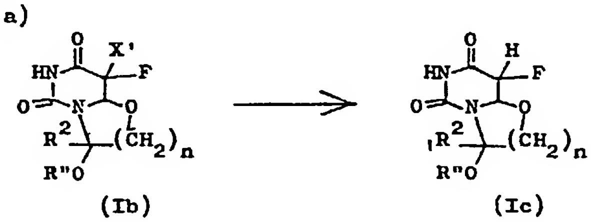
Ozonolysis of the alcohol adduct (III) gives the compounds (Ia), compounds in accordance with the present invention. The reaction may be conducted under conditions employed in conventional ozonolysis. In addition to this process for producing compounds (Ia) directly from compounds (III) by ozonolysis, compounds (Ia) may be prepared via the stable intermediates (IV) by ozonolysis followed by elimination of methanol accompanied by cyclization. The stable intermediate (IV) can be obtained by carrying out the reaction in the presence of methanol.

The acylation or alkylation, for example, of a compound (Ia) according to a known method gives a compound (Ib) in which R^1 is not hydrogen.

The compounds in which Y is not O but NR′, S, SO and SO_2 can be produced in the same way as for the compounds where Y is O.

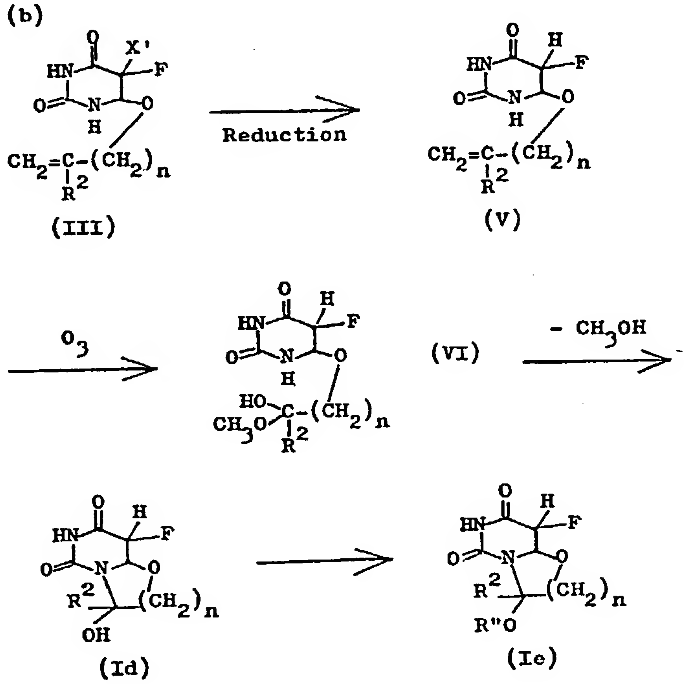
(2) X=hydrogen, Y=O

(a)



In the above general formula (I), compounds in which R[1] is other than hydrogen, X is hydrogen and Y is O can be prepared from compounds (Ib) by reductive elimination of halogen X′. As techniques/conditions for reduction, hydrogenolysis with nickel, palladium, platinum or rhodium catalysts, or hydride reduction with tri-n-butyltin hydride can be employed. Thus, for example, in the case of hydrogenolysis with a palladium catalyst, the reaction may be carried out under conditions of catalytic hydrogenation in tetrahydrofuran, dioxane or a mixture of tetrahydrofuran-methanol in the presence of a weak base such as sodium acetate employing palladium-carbon as a catalyst. Alternatively, reduction with potassium hydrogensulfide (KSH) in an alcohol such as methanol and ethanol may also be employed.

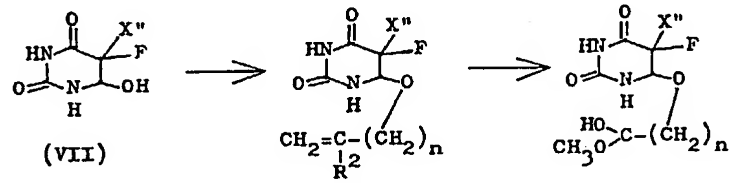
(b)



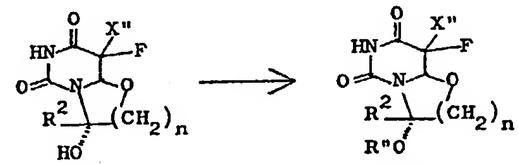
The alcohol substituted derivatives (III) maybe reduced in the san.e manner as described in (a) above, and the subsequent reaction of the resulting compounds (V) may be carried out in a manner analogous to the first mentioned (I) reaction sequence via compounds (IV) to compounds (Ia) and (Ib). The reaction in each step can be conducted in the same manner as is mentioned above.

The reaction(s) in sequences (a) and (b) can also be applied in producing compounds (I) in which Y is not O but NR′, S, SO or SO_2.

(3) X=alkoxycarbonyl, Y=O



(VII) (VIII) (IX)



(If) (Ig)

In the above, X″ is C_2—C_6 alkoxycarbonyl.

The conversion of the starting compounds (VII) to give alcohol substituted compounds (VIII) can be carried out by a substitution reaction analogous to that (1 above) of the unsaturated alcohols

$$CH_2{=}\underset{|}{\overset{R^2}{C}}—(CH_2)_n—OH$$

with compounds (II) (to give compounds (III)). The sequence from alcohol substituted compounds (VIII) to compounds (IX), (If) and (Ig) can be achieved under the same conditions as in the reactions from the compounds (III) to (Ia) and (Ib) (see 1 above). Starting compounds (VII) and the intermediates (VIII) are known compounds, disclosed, for example, Jap. Pat. Unexam. pub. No. 55—102573.

Compounds (I) in which Y is not O but NR′, S, SO and SO_2 can be produced by an analogous procedure to that mentioned above.

The compounds (I) (including Ia-g) of the present invention are orally applicable and have superior anti-tumour action. Thus, for example, the anti-tumour activity of certain compounds (I) against leukemia L1210 in mice as follows.

(Test Method)

Ascites cells (10^5 cell) of leukemia L1210 in mice are diluted with physiological saline and intraperitoneallly implanted in BDF_1 female mice of 5 weeks in age. 8—10 Mice are employed in a control group, and 6—7 mice are employed in a test group to which the test compounds are given. A prefixed compound of the test compounds is administered to the mice of the test group intraperitoneally or orally successively for 5 days.

(Judgement of Effect)

From the average survival days in each test group and control group, the increase of lifespan (ILS) is calculated according to the following equation.

$$\text{ILS (\%)} = \frac{\left(\begin{array}{c}\text{Average survival}\\\text{days in administered}\\\text{group}\end{array}\right) - \left(\begin{array}{c}\text{Average survival}\\\text{days in control}\\\text{group}\end{array}\right)}{\text{(Average survival days in control group)}} \times 100$$

From the dosage having maximum ILS value (maximum effective dose) and 30% ILS value (minimum effective dose), the chemotherapeutic index (CI) is calculated according to the following equation. A higher value indicates higher safety.

$$\text{CI} = \frac{\text{Maximum effective dose (mg/kg)}}{\text{Minimum effective dose (mg/kg)}}$$

(Compounds Tested)

A: 5FU
B: Ftorafur®
C: dl-8α-Fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine
D: dl-8α-Fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine
E: dl-3α-Acetoxy-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine
F: dl-9α-Fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2-H,6H-[1,3]-oxadino[3,2-c]pyrimidine

(Result)

TABLE 1
ILS value (%) of each compound administered intraperitoneally

Dose (mg × day)	Compounds Tested			
	A	B	C	E
4 × 5	20	—	—	—
20 × 5	50	—	—	—
40 × 5	84	0	7	14
100 × 5	13	26	13	18
200 × 5	—	36	32	28
400 × 5	—	4	37	58
600 × 5	—	—	39	—

TABLE 2
CI value of each compound administered intraperitoneally

Compounds	A	B	C	E
Maximum Effective Dose (mg/kg)	200	1000	—	2000
Minimum Effective Dose (mg/kg)	40	700	—	1000
CI Value	5.0	1.4	—	2

TABLE 3
ILS value (%) of each compound administered orally

Dose (mg × day)	Compounds Tested					
	A	B	C	D	E	F
20 × 5	22	—	—	—	—	—
40 × 5	39	1	—	8	1	9
60 × 5	56	—	—	—	—	—
100 × 5	35	19	21	22	−3	13
200 × 5	—	29	47	30	14	32
400 × 5	—	31	59	38	39	51
600 × 5	—	−9	107	51	46	57

TABLE 4
CI value of each compound administered orally

Compounds	A	B	C	D	E	F
Maximum Effective Dose (mg/kg)	300	2000	3000	3000	2400	3000
Minimum Effective Dose (mg/kg)	150	1000	1000	1000	1200	1000
CI Value	2.0	2.0	3.0	3.0	2.0	3.0

As shown by the above results, compounds (I) of the present invention have a superior anti-tumour action and can be applied to humans or animals as anti-tumour agents.

In addition, compounds (I) are advantageous in view of the ease of increase or decrease of dosage, the effective range of the dose being relatively wide.

The compounds (I) can be administered to humans or animals orally or parenterally. Thus, for example, compounds (I) can be administered, e.g. intravenously, intramuscularly or subcutaneously, in various formulation types, e.g. as solutions or suspensions in an appropriate solvent for injection (e.g. distilled water for injection purposes, ethanol, glycerol, propylene glycol, olive oil or peanut oil). In the case of preparations or formulations for injection, compound (I) can be kept in ampoules in the form of solutions of suspensions, or more preferably preserved in ampoules or vials as, e.g. crystals, powder, fine crystals or lyophilizates, and dissolved in water immediately before use. Stabilizers may be added. Moreover, compounds (I) can be administered orally together with pharmaceutical or veterinary components such as diluents (e.g. starch, sucrose, lactose, calcium carbonate or kaolin), lubricants (e.g. stearic acid, sodium benzoate, boric acid, silica or polyethylene glycol) in the forms of, e.g. powder, tablets, granules, capsules, troches or dry syrups.

The invention thus includes a pharmaceutical or veterinary formulation comprising a compound (I) formulated for pharmaceutical or veterinary use, respectively. Such formulations may be in unit dosage form and/or include a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient.

Compounds (I) are generally administered orally at 500 mg—10 g dosage per adult 1 to 3 times a day in the treatment of tumours. The dosage, however, may optionally be increased or decreased according to the age, state, clinical history, etc. of the patient.

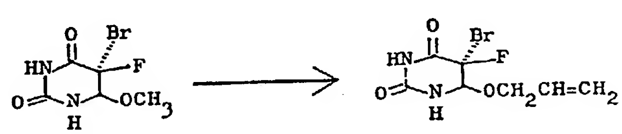
The invention also includes a compound (I) or formulation of the invention for use as an anti-tumour agent in humans or animals.

The following Examples are provided further to illustrate and describe this invention.

EXAMPLE 1

A) dl-5α-Bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxo-6β-(2-propenyloxy)pyrimidine (2):

i)



(1) (2)

dl-5α-Bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-6β-methoxy-2,4-dioxopyrimidine (1)* (89.1 g, 0.37 mol), 2-propen-1-ol (450 ml) and methanesulfonic acid (0.2 ml) are placed in a flask equipped with a Dean-Stark water separator charged with Molecular sieves 4A, and the mixture is stirred under reflux with heating for about 6 hours. The crystalline residue after removal of an excess amount of 2-propen-1-ol under reduced pressure is recrystallized from acetone-ether to give the title compound (2) (80.7 g). Yield: 80.7%, m.p. 196—197°C.

ii)

(3)

A mixture consisting of d1-6β-acetoxy-5α-bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (3)* (2.69 g, 10 mmol), 2-propen-1-ol (30 ml) and methanesulfonic acid (0.1 ml) is stirred under reflux with heating for about 2 hours. After termination of the reaction, the mixture is

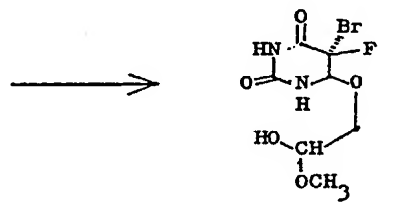
cooled with ice, and sodium bicarbonate (400 mg) is added thereto followed by stirring for 30 minutes. After removal of the insoluble material by filtration, an excess amount of 2-propen-1-ol is distilled off under reduced pressure to give crystalline residue, which is recrystallized from acetone-ether to give the title compound (2) (1.73 g). Yield: 65%. m.p. 196—197°C.

*) Note

dl-5α-Bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-6β-methoxy-2,4-dioxopyrimidine and dl-6β-acetoxy-5α-bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine were produced according to the methods described in the following literature.

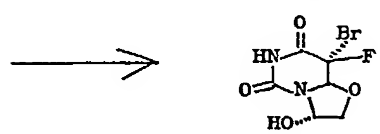
R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenal and J. J. Fox, J. Med. Chem., *10*, 47 (1967)

B) dl-5α-Bromo-5β-fluoro-6β-(2-hydroxy-2-methoxyethoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (4):

(2)  (4)

dl-5β-Fluoro-1,2,3,4,5,6-hexahydro-6β-(2-propenyloxy)2,4-dioxopyrimidine (2) (10 g, 37 mmol) is dissolved in a mixture consisting of dichloromethane (200 ml) and methanol (100 ml), cooled to −78°C in a dry ice-acetone bath, and then the mixture is ozonized by introducing ozone gas. After the reaction mixture turns blue, dimethylsulfide (13.7 ml) is added thereto, and the mixture is warmed up to 0°C and allowed to react for about 1 hour. The crystalline residue after removal of the solvent by distillation is washed with dichloromethane to give the title compound (4) (9.7 g). Yield: 86.4%, m.p. 110—116°C.

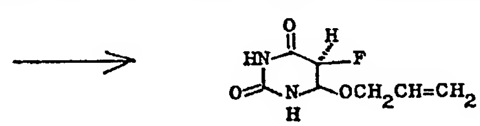
C) dl-8α-Bromo-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (5):

(4)  (5)

Molecular sieves 4A (100 g) is added to the solution of dl-5α-bromo-5β-fluoro-6β-(2-hydroxy-2-methoxyethoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (4) (24 g, 80 mmol) in tetrahydrofuran (530 ml), and the mixture is stirred at room temperature for 4 hours. Molecular sieves 4A is filtrated off, and the solvent is distilled off. The resulting residue is crystallized from a mixture of benzene-ethyl acetate (2:1) to give the title compound (5) (16.1 g). Yield: 75.3%. m.p. 142—143°C.

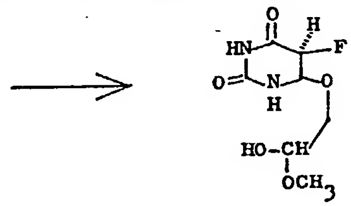
EXAMPLE 2

A) dl-5β-Fluoro-1,2,3,4,5,6-hexahydro-6β-(2-propenyloxy)-2,4-dioxopyrimidine (6):

(2)  (6)

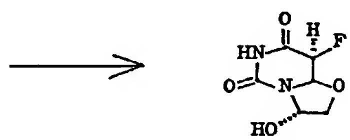
A solution of 86% potassium hydroxide (1.06 g, 22 mmol) dissolved in 2-propen-1-ol (25 ml) is cooled with ice, and hydrogen sulfide (about 700 mg, 20.6 mmol) is absorbed therein. dl-5α-Bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-6β-(2-propenyloxy)-2,4-dioxopyrimidine (2) (4.33 g, 16.2 mmol) is slowly added thereto and allowed to stand at 0°C for 10 minutes, at room temperature for 30 minutes, and at 65°C for 20 minutes successively. The reaction mixture is cooled to room temperature, and the insoluble material is filtered off. Evaporation of the filtrate under reduced pressure gives crystalline residue, which is washed with iced water to give the title compound (6) (2.0 g). Yield: 66%. m.p. 171—172°C.

B) dl-5β-Fluoro-6β-(2-hydroxy-2-methoxyethoxy)-1,2,3,4,5,6-hexahydr-2,4-dioxopyrimidine (7):

(6)  (7)

dl-5β-Fluoro-1,2,3,4,5,6-hexahydro-6β-(2-propenyloxy)-2,4-dioxopyrimidine (6) (3.85 g, 20.4 mmol) is dissolved in a mixture consisting of dichloromethane (150 ml) and methanol (150 ml), cooled to −78°C in a dry ice-acetone bath, and then ozonized by introducing ozone gas. When the reaction mixture turns blue, supply of ozone is stopped, and an excess of ozone is exhausted by introducing nitrogen gas. Dimethylsulfide (40 ml) is added thereto, and the reaction mixture is warmed up to 0°C and allowed to stand overnight. The resulting crystalls are collected by filtration to give the titled compound (7) (2.24 g). Yield: 49.2%. m.p. 176—178°C. The mother liquor is evaporated, and the residue is purified by chromotography over silica gel employing a mixture of benzene-ethyl acetate (1:2) as eluent to give dl-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (8) (359 mg). Yield: 9.2%.

C) dl-8β-Fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (8):

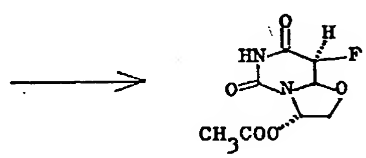
(7)  (8)

Molecular sieves 5A (about 2 g) is added to a solution of dl-5β-fluoro-6β-(2-hydroxy-2-methoxyethoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (7) (520 mg, 2.34 mmol) in tetrahydrofuran (30 ml) and stirred at room temperature for 3 hours. Removal of Molecular sieves 5A by filtration and evaporation of the solvent give crystalline residue, which is recrystallized from ethyl acetate-ether to give the title compound (8) (405 mg). Yield: 91%. m.p. 188—191°C.

Alternatively, the titled compound (8) is obtained in high yield from dl-5β-fluoro-6β-(2-hydroxy-2-methoxyethoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine on elimination of methanol by chromatography over silica gel employing a mixture of benzene-ethyl acetate (1:2) as eluent, as mentioned in Example 2—B).

EXAMPLE 3

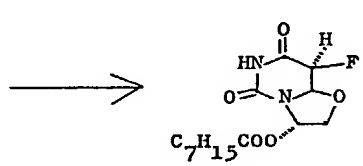
dl-α-Acetoxy-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (9):

(8)  (9)

Acetic anhydride (3 ml) and pyridine (0.5 ml) are added to a solution of dl-8β-fluoro-3α-hydroxy-2,3,6,7,8,6aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (8) (730 mg, 3.8 mmol) in tetrahydrofuran (5 ml), and the mixture is allowed to react at room temperature for 15 hours. The crystalline residue obtained after removal of an excess of reagents and the solvent is recrystallized from acetone-ether to give the title compound (9) (700 mg).
Yield: 78.5%. m.p. 173—174°C.

EXAMPLE 4

dl-8β-Fluoro-2,3,6,7,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (10):

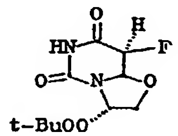
(8)  (10)

Octanoic anhydride (11.5 g, 43 mmol) and pyridine (3.48 ml) are added to a solution of dl-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (8) (2.36 g, 12.4

mmol) in tetrahydrofuran (50 ml), and the mixture is allowed to react at room temperature for 4 hours. After removal of an excess amount of reagents and the solvent, the product is purified by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the title compound (10) (2.61 g).
Yield: 67%. m.p. 58—61°C.

EXAMPLE 5

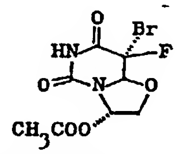
dl-8β-Fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine (11):

(8) ⟶  (11)

dl-8β-Fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (8) (1.9 g, 10 mmol) is dissolved in a mixture solution (70 ml) consisting of acetonitrile and tetrahydrofuran (1:1), and pivalic anhydride (16.2 ml, 80 mmol) is added, and then cooled to 0°C. After tin tetrachloride (1.17 ml, 10 mmol) is added at 0°C in dropwise fashion, the reaction mixture is warmed up to room temperature and stirred for 2 hours. Anhydrous sodium bicarbonate (4.2 g, 50 mmol) and a small amount of water are added thereto, and the mixture is allowed to react at room temperature for 30 minutes. The insoluble material is filtered off, and the solvent is distilled off. The product is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the title compound (11) (270 mg).
Yield: 10%. m.p. 174—175°C.

EXAMPLE 6

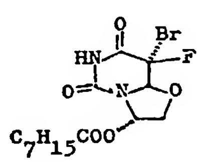
dl-3α-Acetoxy-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (12):

(5) ⟶  (12)

dl-8α-Bromo-8β-fluoro-4α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (5) (2.8 g, 10.4 mmol) is dissolved in acetic anhydride (200 ml), pyridine (10 ml) is added thereto, and then the mixture is allowed to stand at room temperature overnight. After removal of an excesss amount of the reagent under reduced pressure, the product is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (1:1) as eluent to give the title compound (12) (2.09 g). Yield: 65%. m.p. 128—131°C (Crystallized from benzene).

EXAMPLE 7

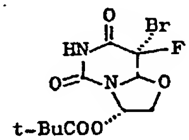
dl-8α-Bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyl-oxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (13):

(5) ⟶  (13)

Octanoic anhydride (11.6 g, 42.8 mmol) and pyridine (1.73 ml, 21.4 mmol) are added to a solution of dl-8α-bromo-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (5) (2.89 g, 10.7 mmol) in tetrahydrofuran (50 ml), and the mixture is allowed to stand at room temperature overnight. The product obtained after removal of an excess amount of reagents and the solvent by distillation is purified by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the title compound (13) (2.94 g). Yield: 69.5%. Oily substance.

EXAMPLE 8

dl-8α-Bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine (14):

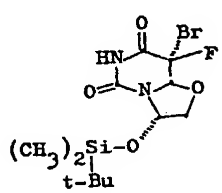
(5) ⟶  (14)

A) dl-8α-Bromo-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (5) (5.26 g, 19.6 mmol) and pivalic anhydride (31.8 ml, 157 mmol) are dissolved in a mixture of tetrahydrofuran (50 ml) and acetonitrile (50 ml), and then tin tetrachloride (2.29 ml, 19.6 mmol) is added under ice cooling in dropwise fashion. The mixture is allowed to stand at room temperature for additional 2 hours, and then sodium bicarbonate (8.23 g, 98 mmol) and a small amount of water are added and stirred well at room temperature for 30 minutes. The insoluble material is filtrated off, and the filtrate is evaporated to dryness under reduced pressure. The oily residue is purified by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1) as eluant to give the title compound (14) (2.79 g). Yield: 40.3%. m.p. 188—189°C (Recrystallized from ether-petroleum ether).

B) dl-8α-Bromo-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (5) (5.25 g, 19.5 mmol), pivalic anhydride (34.2 g, 183 mmol) and pyridine (1.89 ml, 23.4 mmol) are dissolved in tetrahydrofuran (150 ml), and dimethylaminopyridine (1.19 g, 9.8 mmol) is added, and the mixture is allowed to stand at 65°C for 1.5 hours. After removal of an excess amount of reagents and the solvent under reduced pressure, the product is extracted with a mixture of ethyl acetate-acetonitrile. The organic layer is washed with an aqueous sodium bicarbonate and saturated brine, dried on magnesium sulfate, and evaporated. The product is purified by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the title compound (14) (2.45 g).
Yield: 36%.

EXAMPLE 9

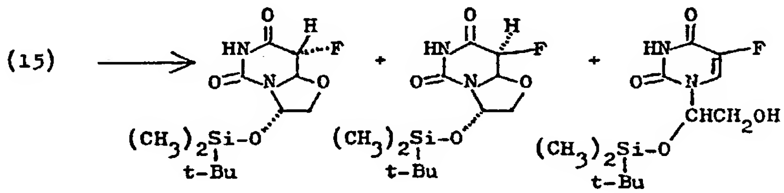
dl-3α-(tert-Butyldimethylsilyloxy)-8α-bromo-8β-fluoro2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (15):

(5) ⟶  (15)

To a solution of tert-butyldimethylsilylimidazolide prepared by adding imidazole (2.39 g, 35.1 mmol) to a solution of tert-butyldimethylsilyl chloride (5.29 g, 3.51 mmol) in dimethylformamide (30 ml) is added a solution of dl-8α-bromo-8β-fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (5) (8.57 g, 31.9 mmol) in dimethylformamide (10 ml), and the mixture is allowed to stand at room temperature for 17 hours. The product is extracted with ethyl acetate. The ethyl acetate layer is washed with saturated brine, dried on magnesium sulfate, and evaporated. The product is purified by chromatography over silica gel employing a mixture of ethyl acetate-benzene (1:2) as eluent to give the title compound (15) (4.77 g).
Yield: 39%. m.p. 152—153°C.

EXAMPLE 10

Catalytic hydrogenation of dl-3α-(tert-butyldimethylsilyloxy)-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (15) — dl-3α-(tert-butyldimethylsilyloxy)-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (16), dl-3α-(tert-butyldimethylsilyloxy)-8β-fluoro-2,3,6,7,8,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (17) and d1-5-fluoro-1-(2-hydroxy-1-tert-butyldimethylsilyloxyethyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine (18):

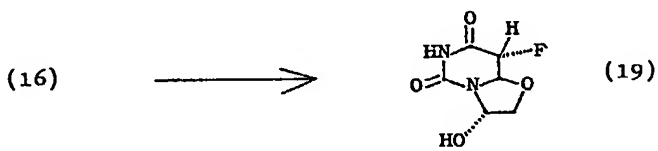


(16) (17) (18)

To a solution of dl-3α-(tert-butyldimethylsilyloxy)-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (15) (4.71 g, 12.3 mmol) in tetrahydrofuran (50 ml) are added sodium acetate (1.11 g, 13.5 mmol) and 10% palladium-carbon (470 mg), and the resulting suspension is hydrogenated under vigorous stirring in hydrogen atmosphere. After about 4 hours a theoretical amount (275 ml) of hydrogen gas is absorbed; the insoluble material is filtered off, and then the solvent is distilled off. The product is separated by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the compound (17) (245 mg) as the first fraction. Yield: 8.1%. m.p. 132—133°C (Recrystallized from methylene chloride-petroleum ether). The compound (16) (1.98 g) is obtained as the main product from the next fraction. Yield: 52.8%. m.p. 165—166°C. (Recrystallized from methylene chloride-petroleum ether). The compound (18) (874 mg) is obtained from the polar fraction.
Yield: 23.4%. m.p. 176—179°C. (Recrystallized from methylene chloride-petroleum ether).

EXAMPLE 11

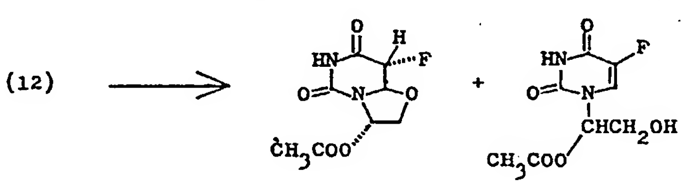
dl-8α-Fluoro-3α-hydroxy-2,3,6,7,8,8aα-hexahydro-5,7-di-oxo-5H-oxazolo[3,2-c]pyrimidine (19):



To a solution of dl-3α(tert-butyldimethylsilyloxy)-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (16) (1.585 g, 5.2 mmol) in acetonitrile (6.6 ml) is added 46% hydrofluoric acid aqueous solution (229 μl), and the mixture is allowed to stand at room temperature for 2 hours. The solvent is evaporated to dryness under reduced pressure, the product is purified by chromatography over silica gel employing a mixture of benzene-ethyl acetate (1:1) as eluent and recrystallized from acetone-ether to give the title compound (19) (753 mg).
Yield: 76%. m.p. 153—158°C.

EXAMPLE 12

dl-3α-Acetoxy-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (20) and dl-5-fluoro-1-(2-hydroxy-1-acetoxyethyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine (21):



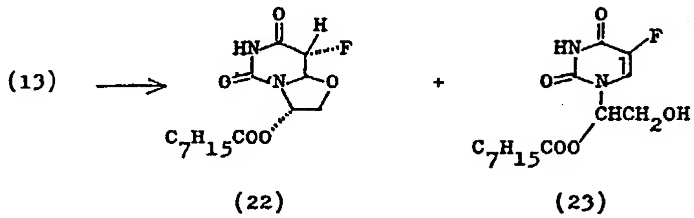
(20) (21)

Anhydrous sodium acetate (946 mg, 11.5 mmol) and 10% palladium-carbon (300 mg) are suspended in a solution of dl-3α-acetoxy-8α-bromo-8β-fluoro-5,7-dioxo-2,3,6,7,8,8aα-hexahydro-5H-oxazolo[3,2-c]pyrimidine (12) (2.99 g, 9.6 mmol) dissolved in tetrahydrofuran (30 ml), and the mixture is catalytically hydrogenated under vigorous stirring in hydrogen atmosphere. After about 3 hours a theoretical amount (215 ml) of hydrogen gas is absorbed; the insoluble material is filtered off,

washed with acetonitrile thoroughly, and then the filtrate is evaporated to dryness. The resulting crystalline residue is crystallized from acetone-methylene chloride to give the title compound (20) (1.08 g). The mother liquor is separated by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (1:1—1:2) as eluent to give the title compound (20) (0.49 g) as an additional crop (Total yield of the compound (20): 1.57 g; Yield: 69%). m.p. 182—185°C. Additionally the compound (21) (0.17 g) is obtained from the polar fraction. Yield: 7.6%. m.p. 280—285°C (Recrystallized from acetone).

EXAMPLE 13

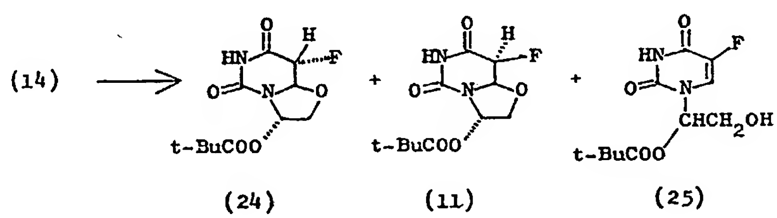
dl-8α-Fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (22) and dl-5-fluoro-1-(2-hydroxy-1-octanoyloxyethyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine (23):



Anhydrous sodium acetate (1.22 g, 14.9 mmol) and 10% palladium-carbon (400 mg) are suspended in a solution of dl-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine (13) (2.94 g, 7.4 mmol) dissolved in tetrahydrofuran (70 ml), and the mixture is catalytically hydrogenated under vigorous stirring in hydrogen atmosphere. After about 4 hours a theoretical amount (167 ml) of hydrogen gas is absorbed; the insoluble material is filtered off, washed with acetonitrile thoroughly, and then the filtrate is evaporated. The resulting crystalline residue is recrystallized from ether-petroleum ether to give the titled compound (22) (0.9 g) as crystals of the first crop. Moreover, the mother liquor is separated by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1—1:1) as eluent to give the title compound (22) (0.6 g) as crystals of the second crop. Total yield of the compound (22): 1.50 g. Yield: 63.7%. m.p. 138—141°C. Additionally, the compound (23) (0.16 g) is obtained from the polar fraction. Yield: 6.8% m.p. 107—111°C (Recrystallized from acetone-ether).

EXAMPLE 14

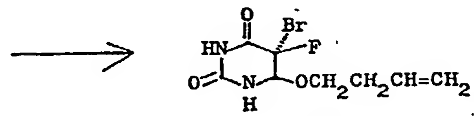
Catalytic hydrogenation of dl-8α-bromo-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine (14) — dl-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine (24, dl-8β-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethylacetoxy-5H-oxazolo[3,2-c]pyrimidine (11) and dl-5-fluoro-(2-hydroxy-1-trimethylacetoxyethyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine (25):



Anhydrous sodium acetate (1.39 g, 17 mmol) and 10% palladium-carbon (0.5 g) are suspended into a solution of the title compound (14) (5.0 g, 14.2 mmol) dissolved in tetrahydrofuran (50 ml), and the mixture is catalytically hydrogenated under vigorous stirring in hydrogen atmosphere. After about 3 hours a theoretical amount (320 ml) of hydrogen gas is absorbed; the insoluble material is filtrated off, and then the filtrate is evaporated. The resulting crystalline residue is recrystallized from acetone-ether to give the compound (24) (2.02 g). Yield: 52.0%. The mother liquor is separated by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1—1:1) as eluent to give the compound (11) (372 mg) as the first fraction. Yield: 9.6%. m.p. 176—177°C (Recrystallized from acetone-ether). The compound (24) (480 mg) is obtained as the main product from the next fraction. Total amount of the compound (24): 2.50 g. Total yield: 64.4%. m.p. 164—166°C (Recrystallized from acetone-ether). Additionally, the compound (25) (20 mg) is obtained from the polar fraction. Yield: 0.5%. m.p. 151—152°C (Recrystallized from acetone-ether).

EXAMPLE 15

A) dl-5α-Bromo-6β-(3-butenyloxy)-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (26):

(i) 

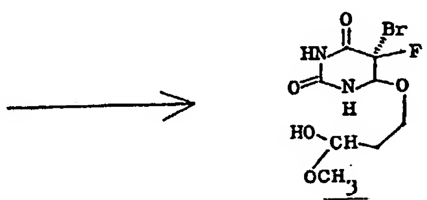
(26)

dl-5α-Bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-6β-methoxy-2,4-dioxopyrimidine (1) (50 g. 207 mmol), 3-buten-1-ol (27 ml, 310 mmol) and methanesulfonic acid (5 ml) are dissolved in acetonitrile (500 ml), placed in a flask equipped with a Dien-Stark water separator charged with Molecular sieves 4A (60 g), and then refluxed with heating for 4 hours. After cooling, the product is extracted with ether. The ether layer is washed with an aqueous sodium bicarbonate and saturated brine, dried on magnesium sulfate, and the solvent is distilled off. The resulting crystals are washed with water several times and then dried to give the title compound (26) (36 g). Yield: 72%.

ii) (3) → (26)

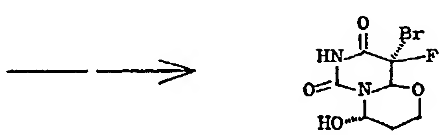
To a solution of dl-6β-acetoxy-5α-bromo-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (3) (30 g, 110 mmol) and 3-buten-1-ol (14.6 ml, 165 mmol) dissolved in acetonitrile (500 ml) is added methanesulfonic acid (1 ml), and the mixture is allowed to stand at 70—80°C for 3 hours. The solvent and an excess amount of the reagent are evaporated, and water is added to the residue to give crystalline product. The product is collected by filtration, washed with water several times and dried to give the title compound (26) (21.5 g). Yield: 70%. m.p. 136.5—139°C (Recrystallized from ether-petroleum ether).

B) dl-5α-Bromo-5β-fluoro-6β-(3-hydroxy-3-methoxypropoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (27):

(26)  (27)

dl-5α-Bromo-6β-(3-butenyloxy)-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (26). (21.5 g, 77 mmol) is dissolved in a mixture solution of dichloromethane (400 ml) and methanol (200 ml), cooled to —70°C in a dry ice-acetone bath and ozonized by introducing ozone gas. When the reaction mixture turns blue, supply of ozone is stopped, and an excess amount of ozone is exhausted by introducing nitrogen gas; then dimethylsulfide (41 ml) is added thereto, and the mixture is allowed to stand at 0°C for 15 hours. The product obtained by removal of the solvents is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (1:1—1:2) as eluent to give the title compound (27) (15.4 g). Yield: 63%. m.p. 99—102°C.

C) dl-9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino-[3,2-c]pyrimidine (28):

(27)  (28)

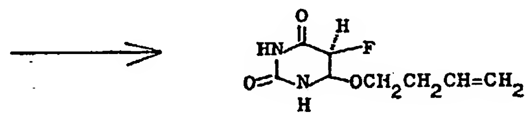
dl-5α-Bromo-5β-fluoro-6β-(3-hydroxy-3-methoxypropoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (27) 5.0 g, 15.9 mmol) is dissolved in acetone (30 ml) and water (30 ml), and 60% perchloric acid aqueous solution (5 ml) is added thereto; the mixture is allowed to stand at room temperature for 3 hours. After the reaction mixture is neutralized with sodium carbonate, the solvent is distilled off under reduced pressure. The remaining moisture is removed by azeotropic distillation with benzene as much as possible. Ether is added to the residue to extract the product, and sodium perchlorate which is insoluble in ether is removed by filtration. After removal of the solvent, the ether extract is purifed by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (1:1) as eluent to give the title compound (28) (2.93 g). Yield: 65%. m.p. 137.5—139.5°C (Recrystallized from ether).

The mother liquor (about 9.3 g) after crystallization of dl-5α-bromo-5β-fluoro-6β-(3-hydroxy-3-methoxypropoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (27) obtained by the above mentioned ozonization reaction is dissolved in acetone (50 ml) and water (50 ml), and allowed to react with 60% aqueous perchloric acid (8.3 ml) at room temperature for 4 hours. The reaction mixture is worked up in the same manner as mentioned above to give the title compound (28) (4.19 g). Overall yield of the title compound (28) produced from d1-5α-bromo-6β-(3-butenyloxy)-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (26) (21.5 g) is 13.2 g. Yield: 60.6%.

EXAMPLE 16

A) dl-5β-Fluoro-6β-(3-butenyloxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (29):

(26)

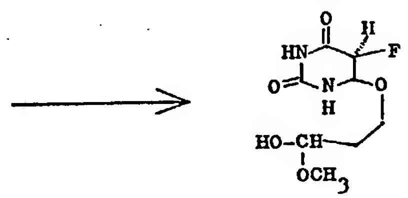


(29)

A solution of 86% potassium hydroxide (5.05 g, 77.4 mmol) dissolved in methanol (180 ml) is cooled to −5°C, and hydrogen sulfide (3.34 g, 98.3 mmol) is absorbed therein. dl-5α-Bromo-6β-(3-butenyloxy)-5β-fluoro-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (26) (22.9 g, 81.5 mmol) is added thereto and allowed to react at −5°C for 10 minutes, at room temperature for 30 minutes, and then at 60°C for 10 minutes, successively. After cooling, the reaction mixture is neutralized with sodium bicarbonate, and the insoluble material is filtered off and washed with acetone. The filtrate is evaporated, and the crystalline residue is crystallized from acetone-petroleum ether to give the title compound (29) (8.2 g). Yield: 53%. m.p. 167—169°C.

B) dl-5β-Fluoro-6β-(3-hydroxy-3-methoxypropoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (30):

(29)

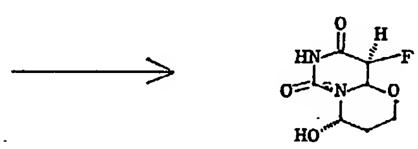


(30)

dl-5β-Fluoro-6β-(3-butenyloxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (29) (10.2 g, 50.4 mmol) is dissolved in a mixture of dichloromethane (200 ml) and methanol (100 ml), cooled to −70°C in a dry ice-acetone bath, and ozonized by introducing ozone gas. When the reaction mixture turns blue, supply of ozone is stopped, and an excess amount of ozone is exhausted by introducing nitrogen gas. Dimethyl sulfide (32 ml) is added thereto, and the mixture is allowed to stand at 0°C for 1 hour. The solvent is removed by distillation, and the residue is dissolved in a mixture of benzene-ethyl acetate (1:2), passed through a silica gel column to remove dimethylsulfoxide and then evaporated to give the title compound (30) (7.78 g) as an oily crude product. The obtained product containing a small amount of the compound (30) is subjected to the following reaction.

C) dl-9β-Fluoro-4α-hydroxy-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (31):

(30)



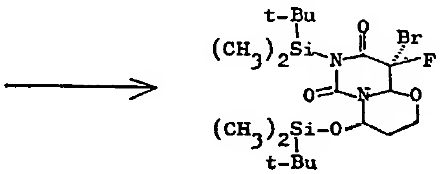
(31)

The crude dl-5β-fluoro-6β-(3-hydroxy-3-methoxypropoxy)-1,2,3,4,5,6-hexahydro-2,4-dioxopyrimidine (30) obtained in B) is dissolved in a mixture of acetone (50 ml) and water (50 ml), to which conc. sulfuric acid (1 ml) is added, and allowed to stand at room temperature for 1 hour. The reaction mixture is neutralized with sodium carbonate, and the solvent is distilled off under reduced pressure. The residue is extracted with acetone to remove sodium sulfate produced, and the acetone extract is passed through a short column of silica gel. The eluate with acetone is evaporated, and the residue is recrystallized from acetone-ether to give the title compound (31) (3.73 g). Yield from the compound (29): 36%. m.p. 126—128°C.

EXAMPLE 17

dl-4α-(tert-Butyldimethylsilyloxy)-7-tert-butyldimethylsilyl-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (32):

(28)



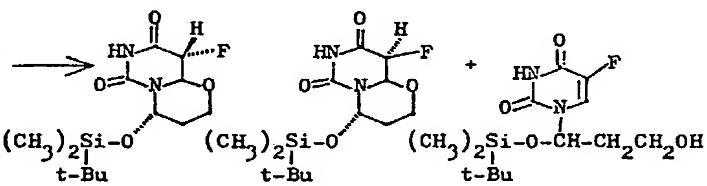
(32)

To a solution of tert-butyldimethylsilylimidazolide prepared by adding imidazole (5.61 g, 82.5 mmol) to a solution of tert-butyldimethylsilyl chloride (8.29 g, 55 mmol) in dimethylformamide (120 ml) is added dl-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (28) (6.25 g, 22 mmol), and the mixture is allowed to stand at room temperature for 2.5 days. The product is extracted with ethyl acetate, and the ethyl acetate layer is washed with water, dried on magnesium sulfate, and evaporated. The residue is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (9:1) as eluent to give the title compound (32) (6.06 g). Yield: 54%. m.p. 152—155°C.

EXAMPLE 18

Catalytic hydrogenation of dl-4α-(tert-butyldimethylsilyloxy)-7-tert-butyldimethylsilyl-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (32):

(32)



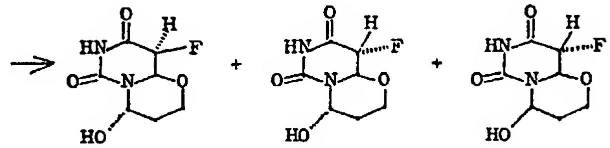
(33) (34) (35)

To a solution of the comound (32) (6.06 g, 11.9 mmol) dissolved in tetrahydrofuran (60 ml) are added 10% palladium-carbon (300 mg) and anhydrous sodium acetate (1.38 g, 16.8 mmol), and the mixture is hydrogenated under vigorous stirring in hydrogen atmosphere. After about 4 hours a theoretical amount (533 ml) of hydrogen gas is absorbed; insoluble material is filtered off and washed with acetonitrile. The filtrate is evaporated, and the residue is separated by chromatography over silica gel employing a mixture of benzene-ethyl acetate (4:1—1:2) as eluent to give a mixture (3.06 g, Yield: 81%) of dl-4α-(tert-butyldimethylsilyloxy)-9α-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (33) and dl-4α-(tert-butyldimethylsilyloxy)-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (34) (about 3:2), and from the polar fraction dl-5-fluoro-1-(3-hydroxy-1-tert-butyldimethylsilyloxypropyl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidine (35) (331 mg, Yield: 8.7%). m.p. 131—133°C.

EXAMPLE 19

dl-9β-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (31), dl-9α-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (36) and dl-9α-fluoro-3,4,7,8,9,9aα-hexahydro-4β-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (37):

(33) + (34)



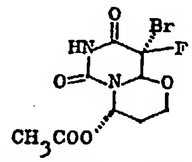
(31) (36) (37)

To a solution of a mixture (2.64 g, 8.29 mmol) of dl-9α and 9β-fluoro-4α-(tert-butyldimethylsilyloxy)-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (33) and (34) dissolved in acetonitrile (12 ml) is added 4.6% aqueous hydrofluoric acid (381 μl) and allowed to stand at room temperature for 2 hours. The solvent is removed by distillation to give residue, of which the acetone soluble part (1.61 g) is separated by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (1:2) as eluent to give at first the title compound (37) (m.p. 232—234°C, recrystallized from acetone-ether) and subsequently the title compound (36) (m.p.

148—152°C, recrystallized from acetone-ether) and finally the title compound (31) (m.p. 126—128°C, recrystallized from acetone-ether).

EXAMPLE 20

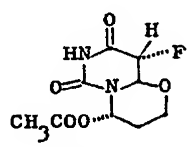
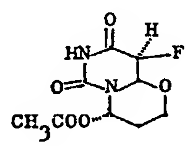
dl-4α-Acetoxy-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (38):

(28) ⟶  (38)

dl-9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxamino[3,2-c]pyrimidine (28) (14.4 g, 50.9 mmol) is added to acetic anhydride (210 ml) and pyridine (4.1 ml, 50.9 mmol), and allowed to stand at room temperature for 15 hours. An excess amount of the reagents is distilled off, and the residue is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (3:1) as eluent to give the title compound (38) (10.59 g). Yield: 64%. m.p. 171—174°C (Recrystallized from benzene).

EXAMPLE 21

dl-4α-Acetoxy-9α-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]-pyrimidine (39) and dl-4α-acetoxy-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (40):

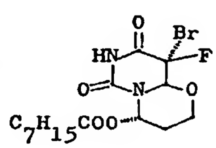
(38) ⟶  + 

(39) (40)

Anhydrous sodium acetate (2.57 g, 31.3 mmol) and 10% palladium-carbon (500 mg) are added to a solution of dl-4α-acetoxy-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (38) (8.48 g, 26.1 mmol) dissolved in tetrahydrofuran (100 ml), and the mixture is catalytically hydrogenated under vigorous stirring in hydrogen atmosphere. After about 4 hours a theoretical amount (585 ml) of hydrogen gas is absorbed; the insoluble material is filtered off and then washed with acetonitrile. The filtrate is evaporated, and the residue is separated by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (1:1) as eluent to give dl-4α-acetoxy-9α-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (39) (2.55 g, Yield: 39.7%. m.p. 150—154°C) and dl-4α-acetoxy-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (40) (1.37 g, Yield: 21.3% m.p. 153.5—155.5°C).

EXAMPLE 22

dl-9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-octanoyloxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (41):

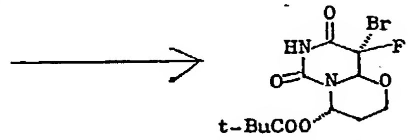
(28) ⟶  (41)

Dimethylaminopyridine (499 mg, 4 mmol) is added to a solution of dl-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (28) (2.31 g, 8.1 mmol), octanoic anhydride (8.83 g, 32.4 mmol) and pyridine (0.66 ml, 8.1 mmol) dissolved in tetrahydrofuran (40 ml), and the mixture is allowed to stand at room temperature for 15 hours. The solvent is evaporated, and the residue is separated and purified by chromatography on a silica gel column employing a mixutre of benzene-ethyl acetate (4:1) as eluent, and recrystallized from ether-petroleum ether to give the title compound (41) (1.29 g). Yield: 38.9%. m.p. 108—110°C.

EXAMPLE 23

dl-9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (42):

(28)



(42)

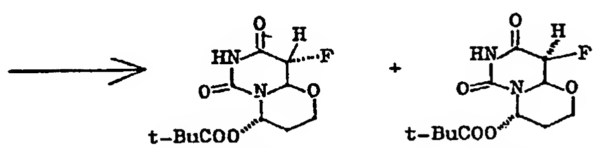
i) dl-9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (28) (820 mg, 2.9 mmol) and pivalic anhydride (4.7 ml, 23.2 mmol) are dissolved in a mixture of tetrahydrofuran (2 ml) and acetonitrile (8 ml), and tin tetrachloride (0.33 ml, 2.9 mmol) is added in dropwise fashion under ice cooling. The mixture is stirred at room temperature for additional 2 hours, and sodium bicarbonate (1.34 g, 16 mmol) and a small amount of water are added and stirred well at room temperature for 30 minutes. The insoluble material is filtred off, and the filtrate is evaporated to dryness under reduced pressure. The oily residue is purified by chromatography over silica gel employing a mixture of benzene-ethyl acetate (2:1) as eluent to give the title compound (42) (186 mg). Yield: 16%. m.p. 178—179°C (Recrystallized from tetrahydrofuran-acetone).

ii) dl-9α-Bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (28) (10 g, 35.3 mmol), pivalic anhydride (46 ml, 226 mmol) and pyridine (2.86 ml, 35.3 mmol) are dissolved in tetrahydrofuran (70 ml), and dimethylaminopyridine (2.16 g, 17.7 mmol) is added thereto and allowed to stand at room temperature for 4 hours. The precipitated insoluble material is filtered off, and filtrate is concentrated. The product is crystallized from tetrahydrofuran-acetone to give the title compound (41) (4.84 g). Moreover, the mother liquor is separated and purified by chromatography on a silica gel column employing a mixture of benzene-acetone (2:1) to give the title compound (42) (0.95 g) as an additional crop. Total amount: 5.79 g. Yield: 44.7%. m.p. 178—179.5°C (Recrystallized from tetrahydrofuran-acetone).

EXAMPLE 24

dl-9α-Fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (43):

(42)



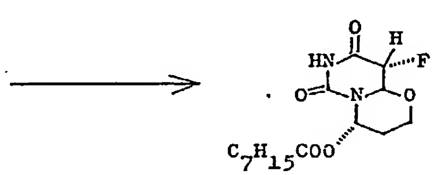
(43) (46)

To a solution of dl-9α-bromo-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (42) (6.0 g, 16.3 mmol) in a mixture of methanol (50 ml) and tetrahydrofuran (240 ml) are added anhydrous sodium acetate (2 g, 24.5 mmol) and 10% palladium-carbon (600 mg), and the mixture is catalytically hydrogenated under vigorous stirring in hydrogen atmosphere. After about 1 hour a theoretical amount (365 ml) of hydrogen gas is absorbed; the insoluble material is filtered off and washed with acetonitrile. The solvent is distilled off, and the residue is extracted with a mixture of ethyl acetateacetonitrile. The organic layer is washed with an aqueous sodium bicarbonate solution and saturated brine and dried on magnesium sulfate, and then evaporated to dryness. The residue is recrystallized from acetone-ether to give the title compound (43) (1.84 g). Yield: 39.2%. m.p. 163—166°C. The mother liquor contains the title compound (43) and its 9β-fluoro-epimer i.e., dl-9β-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethylacetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (46). The ratio of two isomers, 9α-fluoro to 9β-fluoro derivatives produced by catalytic hydrogenation is about 3:2, which is determined by NMR spectrum.

EXAMPLE 25

dl-9α-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-octanoyloxy-6, 8-dioxo-2H,6H-[1,3]oxazino[3,2-c]pyrimidine (44):

(36)



(44)

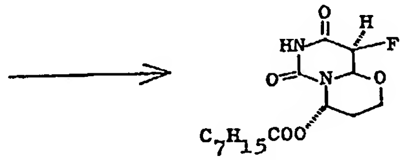
dl-9α-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (36) (408 mg, 2 mmol), octanoic anhydride (2.7 g, 10 mmol) and pyridine (1 ml, 12.7 mmol) are dissolved in tetrahydrofuran (5 ml) and allowed to stand at room temperature for 15 hours.

An excess amount of reagents and the solvent are removed by distillation under reduced pressure, and the product is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the title compound (44) (423 mg). Yield: 64%. m.p. 85—86°C.

EXAMPLE 26

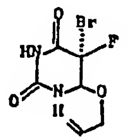
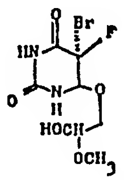
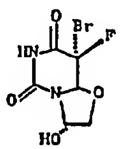
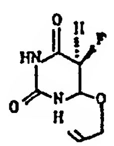
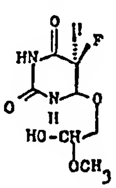
dl-9β-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-octanoyloxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (45):

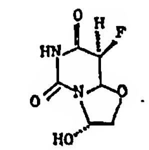
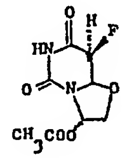
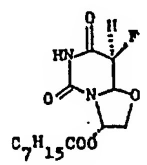
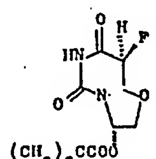
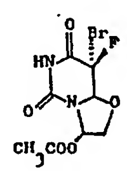
(31)

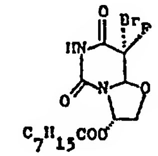
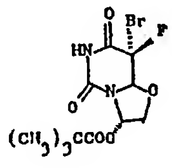
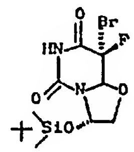
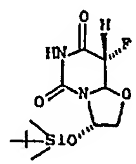
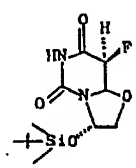


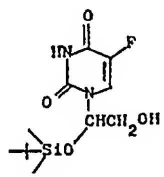
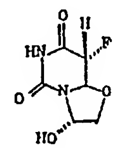
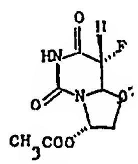
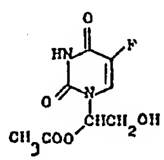
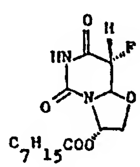
(45)

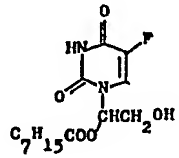
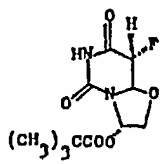
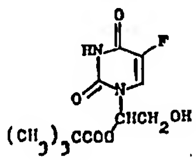
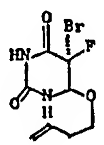
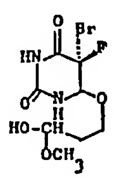
dl-9β-Fluoro-3,4,7,8,9,9aα-hexahydro-4α-hydroxy-6,8-dioxo-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine (31) (100 mg, 0.49 mmol), octanoic anhydride (460 mg, 1.7 mmol) and pyridine (0.048 ml, 0.59 mmol) are dissolved in tetrahydrofuran (2 ml) and allowed to stand at room temperature for 15 hours. An excess amount of reagents and the solvent are removed by distillation under reduced pressure, and the product is purified by chromatography on a silica gel column employing a mixture of benzene-ethyl acetate (4:1) as eluent to give the title compound (45) (100 mg). Yield: 62%. Oily substance.

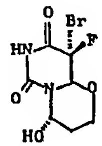
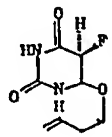
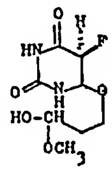
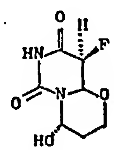
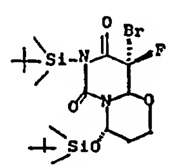
Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
2		mp 196—197°C $C_7H_8BrFN_2O_3$ (267.07) Anal. C H N F cal. 31.48 3.02 10.49 7.11 F 31.21 2.96 10.47 7.57	IR(KBr) 3250, 1754, 1717 cm^{-1}	4.27(2H,m), 5.5—5.1(3H,m), 6.3—5.6(1H,m), 8.08(1H,br), 9.87(1H,br)
4		mp 110—116°C $C_7H_{10}BrFN_2O_5$ (301.086) Anal. C H N F cal. 27.92 3.35 9.31 6.31 F 28.02 3.47 9.16 6.58	(IR(KBr) 3360, 3240, 1740, 1717 cm^{-1}	3.35(3H,S), 3.68(2H,d,J=5Hz), 4.68(1H,m), 5.35(1H,d,J=4.5Hz), 8.13(1H,br), 9.83(1H,br) (+CO_3OD) 3.35(3H,S), 3.67(2H,d,J=5Hz), 4.67(1H,t,J=5Hz),5.35(1H,S)
5		mp 142—143°C $C_6H_6BrFN_2O_4$ (269.044) Anal. C H N F cal. 26.78 2.25 10.41 7.06 F 27.08 2.42 10.25 7.16	IR(KBr) 3450, 3225, 1740, 1720 cm^{-1}	4.03(1H,dd,J=1&9Hz), 4.37(1H,dd, J=4&9Hz), 5.78(1H,d,J=18Hz), 5.97(1H,m)
6		mp 171—172°C $C_7H_9FN_2O_3$ (188.162) Anal. C H N F cal. 44.68 4.82 14.89 10.10 F 44.55 4.64 14.87 10.10	IR(KBr) 3230, 1758, 1716 cm^{-1}	4.17(2H,m), 5.5—4.9(4H,m), 6.2—5.6(1H,m), 7.9(1H,br), 9.4(1H,br)
7		mp 176—178°C $C_7H_{11}FN_2O_5$ (222.18) Anal. C H N F cal. 37.84 4.99 12.61 8.55 F 37.58 4.76 12.83 8.69	IR(KBr) 3330, 1740, 1725 cm^{-1}	3.35(3H,S), 3.60(2H,d,J=5Hz), 4.67(1H,m), 4.93—5.33(2H,m), 5.47(1H,dd,J=4&36Hz), 7.8(1H,br), 11.0(1H,br) (+D_2O) 3.37(3H,S), 3.61(2H,d,J=5Hz), 4.7(1H,t,J=5Hz), 5.10(1H,dd,J=4&6Hz), 5.50(1H,dd,J=4&40Hz)

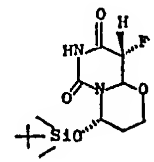
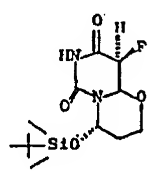
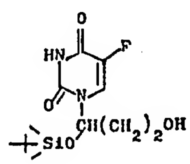
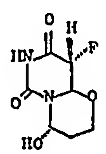
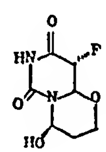
Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
8		mp 188—191°c $C_6H_7FN_2O_4$ (190.136) Anal. C H N F cal. 37.90 3.71 14.74 9.99 F 37.84 3.73 14.77 9.98	IR(KBr) 3395, 3246, 1738, 1677 cm^{-1}	3.93(1H,dd,J=2&9Hz), 4.28(1H,dd,J=4&9Hz), 4.98(1H,dd,J=2&51Hz), 5.65(1H,dd,J=2&24Hz), 5.87(1H,m), 8.8—12(1H,br)
9		mp 173—174°C $C_8H_9FN_2O_5$(232.172) Anal. C H N F cal. 41.38 3.91 12.07 8.18 F 41.56 3.97 11.86 8.38	IR(KBr) 3220, 1740, 1702 cm^{-1}	2.07(3H,S), 4.10(1H,dd,J=2&10Hz), 4.40(1H,ddd,J=0.5, 4&10Hz), 5.06(1H,dd,J=2&50Hz), 5.[illegible] dd,J=2&24Hz), 6.68(1H,[illegible] 2&4Hz), 10.0(1H,br)
10		mp 58—61°C $C_{14}H_{21}FN_2O_5$ (316.33) Anal. C H N F cal. 53.15 6.69 8.86 6.01 F 53.21 6.70 8.86 6.04	IR(KBr) 3270, 1740, 1723 cm^{-1}	0.87(3H,t,J=6Hz), 1.0—2.[illegible] CH,m), 2.37(2H,t,J=6Hz), 4.12(1H,dd,J=2&10Hz), 4.42(1H,dd,J=4&10Hz), 5.08(1H,dd,J=2&50Hz), 5.80(1H,dd, J=2&24Hz), 6.72(1H,dd,J=2&4Hz), 9.83(1H,br)
11		mp 176—177°C $C_{11}H_{15}FN_2O_5$ (274.25) Anal. C H N F cal. 48.17 5.51 10.22 6.93 F 48.06 5.39 10.26 7.06	IR(KBr) 3290, 1723(br)	1.20(9H,S), 4.08(1H,dd,J=2&10Hz), 4.45(1H,dd,J=4&10Hz), 5.08(1H,dd,J=2&50Hz), 5.82(1H, dd,J=2&24Hz), 6.70(1H,dd,J=2&4Hz)
12		mp 128—131°C $C_8H_8BrFN_2O_5$ (311.08) Anal. C H N F cal. 30.89 2.59 9.00 6.11 F 31.24 2.67 8.92 6.50	IR($CHCl_3$) 3370, 1745 cm^{-1}	2.10(3H,S), 4.20(1H,dd,J=1&10Hz), 4.47(1H,ddd,J=0.5,4&10Hz), 5.75(1H,d,J=18Hz), 6.75(1H,dd,J=1&4Hz), 9.5—12.8(1H,br)

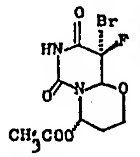
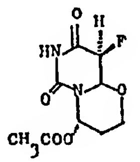
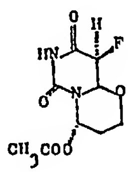
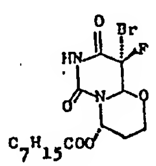
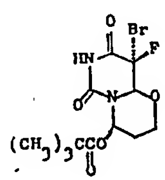
Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
13		oil $C_{14}H_{20}BrFN_2O_5$ (395.236)	IR($CHCl_3$) 3370, 1740 cm^{-1}	0.90(3H,t,J=5Hz), 2.30(2H,t,J=6Hz), 1.0—2.0(10H,m), 4.18(1H,dd,J=1&10Hz), 4.47(1H,ddd,J=0.5,4&10Hz), 5.88(1H,d,J=19Hz), 6.77 (1H,dd,J=1&4Hz)
14		mp 188—189°C $C_{11}H_{14}BrFN_2O_5$ (353.156) Anal. C H N F cal. 37.41 4.00 7.93 5.38 F 37.35 3.81 7.87 5.58	IR($CHCl_3$) 3370, 1740 cm^{-1}	1.20(9H,S), 4.15(1H,dd,J=1&9Hz), 4.47(1H,ddd,J=0.5,4&9Hz), 5.95(1H,d,J=18Hz), 6.77(1H,dd,J=1&4Hz)
15		mp 152—153°C $C_{12}H_{20}BrFN_2O_4Si$ (383.302) Anal. C H N F cal. 25.13 3.52 4.89 3.31 F 25.37 3.21 5.03 3.22	IR(KBr) 1756, 1692 cm^{-1}	(CD_3Cl) 0.13(3H,S), 0.22(3H,S),0.92(9H,S), 4.03(1H,dd,J=1&8Hz), 4.28(1H,dd,J=4&8Hz), 5.60(1H,d,J=18Hz), 5.98(1H,dd,J=1&4Hz), 8.4(1H,br)
16		mp 165—166°C $C_{12}H_{21}FN_2O_4Si$ (304.396) Anal. C H N F cal. 47.35 6.95 9.20 6.24 F 47.45 7.18 9.14 6.51	IR(KBr) 1752, 1715(sh) 1688 cm^{-1}	0.16(3H,S), 0.22(3H,S), 0.90(9H,S), 3.90(1H,dd,J=1.5&9Hz), 4.32(1H,dd,J=4.5&9Hz), 5.07(1H,dd, J=8.5&50.3Hz), 5.60(1H,dd,J=8.5&10Hz), 5.87(1H,m)
17		mp 132—133°C $C_{12}H_{21}FN_2O_4Si$ (304.396) Anal. C H N F cal. 47.35 6.95 9.20 6.24 F 47.52 7.18 9.13 6.23	IR(KBr) 1736, 1698 cm^{-1}	0.13(3H,S), 0.23(3H,S), 0.92(9H,S), 3.95(1H,dd,J=8&1Hz), 4.25(1H,dd,J=8&4Hz), 5.00(1H,dd,J=50&2Hz), 5.70(1H,dd,J=24&2Hz), 5.98(1H,dd,J=1&4Hz), 9.67(1H,br)

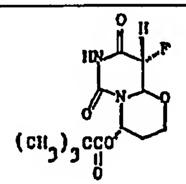
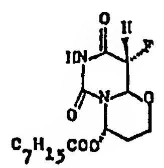
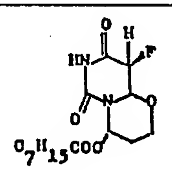
Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
18		mp 176—179°C $C_{12}H_{21}FN_2O_4Si$ (304.396) Anal. C H N F cal. 47.35 6.95 9.20 6.24 F . 47.19 7.04 9.02 6.51	IV:λ_{max}^{EtOH}269mμ (ε=8,770) IR(KBr) 3400, 1710(br), 1660 cm^{-1}	0.10(3H,S), 0.17(3H,S), 0.92(9H,S), 3.73(2H,d,J=6Hz), 6.03(1H,dt,J=2&6Hz), 7.80(1H,d,J=7Hz)
19		mp 153—158°C $C_8H_7FN_2O_4$(190.136) Anal. C H N F cal. 37.90 3.71 14.74 9.99 F 37.79 3.70 14.68 10.33	IR(KBr) 3470, 1735, 1700 cm^{-1}	3.85(1H,dd,J=3&9.5Hz), 4.37(1H, dd,J=5&9.5Hz), 5.08(1H,dd,J=8.5&49Hz), 5.58(1H,dd,J=8.5&11Hz), 5.80(1H,m)
20		mp 182—185°C $C_8H_9FN_2O_5$ (232.172) Anal. C H N F cal. 41.39 3.91 12.07 8.18 F 41.12 4.12 11.07 8.15	IR(Nujol) 1755 (sh), 1740, 1700 cm^{-1}	2.07(3H,S), 2.79(1H,br), 4.09 (1H,dd,J=2&10Hz), 4.47(1H,dd, J=4.5&10Hz), 5.30(1H,dd,J=8.5&48.8Hz), 5.59(1H,dd,J=8.5&12Hz), 6.58(1H,ddd,J= 2,3&4.5Hz)
21		mp 280—285°C $C_8H_9FN_2O_5$ (232.172) Anal. C H N F cal. 41.38 3.91 12.07 8.18 F 41.44 3.99 11.93 8.10	VV:λ_{max}^{EtOH}266mμ (ε=8,300) IR(Nujol) 3500, 3200—3500, 1755, 1705, 1663 cm^{-1}	2.13(3H,S), 3.87(2H,d,J=5Hz), 6.77(1H,dt,J=2&5Hz), 7.85(1H,d,J=7Hz)
22		mp 138—141°C $C_{14}H_{21}FN_2O_5$ (316.33) Anal. C H N F cal. 53.15 6.69 8.86 6.01 F 52.51 6.51 8.82 5.96	IR($CHCl_3$) 3370, 1735 cm^{-1}	0.87(3H,t,J=5Hz), 1.0—2.0(10H,m), 2.35(3H,t,J=6Hz), 4.01(1H,dd,J=2&9Hz), 4.50(1H,dd,J=4&9Hz), 5.18(1H,dd,J= 8.5—50.4Hz), 5.68(1H,dd,J=8.5&9.6Hz), 6.58(1H,m)

Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
23		mp 107—111°C $C_{14}H_{21}FN_2O_5$ (316.33) Anal. C H N F cal. 53.16 6.69 8.86 6.01 F 52.88 6.65 8.78 5.77	VV:λ_{max}^{EtOH}266.5 mμ(ε=8,500) IR($CHCl_3$) 3360, 3600—3300, 1757, 1710, 1670 cm^{-1}	0.88(3H,t,J=5Hz), 1.1—1.9(10H,m), 2.45(2H,t,J=7Hz), 3.93(2H,d,J=5Hz), 6.80(1H,dt,J=1&5Hz), 7.85(1H,d,J=7Hz)
24		mp 164—166°C $C_{11}H_{15}FN_2O_5$ (274.25) Anal. C H N F cal. 48.17 5.51 10.22 6.93 F 47.43 5.30 10.08 6.70	IR($CHCl_3$) 3380, 1740 cm^{-1}	1.20(9H,S), 4.00(1H,dd,J=2&10 Hz), 4.52(1H,dd,J=5&10Hz), 5.18(1H,dd,J=8&51.5Hz), 5.67(1H,dd,J=8&8.5Hz), 6.57(1H,m)
25		mp 151—152°C $C_{11}H_{15}FN_2O_5$ (274.25) Anal. C H N F cal. 48.17 5.51 10.22 6.93 F 47.83 5.43 10.21 7.02	VV:λ_{max}^{MeOH}266mμ (ε=8,500) IR($CHCl_3$) 3380, 3550—3300, 1750, 1715 cm^{-1}	1.22(9H,S), 3.90(2H,d,J=5Hz), 6.73(1H,dt,J=2&5Hz), 7.82(1H,d,J=7Hz)
26		mp 136.5—139°C $C_8H_{10}BrFN_2O_3$ (281.096) Anal. C H N F cal. 34.18 3.59 9.97 6.76 F 33.86 3.49 9.88 6.91	IR(Nujol) 1756, 1704 cm^{-1}	2.33(2H,m), 3.83(2H,m), 5.4—5.9(3H,m), 5.5—6.2(1H,m), 8.25(1H,br)
27		mp 99—102°C $C_8H_{12}BrFN_2O_5$ (315.112) Anal. C H N F cal. 30.49 3.84 8.89 6.03 F 30.24 3.60 9.02 6.16	IR($CHCl_3$) 3380, 3100—3500, 1740 cm^{-1}	1.53—2.1(2H,m), 3.33(3H,S), 3.7—4.2(2H,m), 4.40(1H,t,J=6Hz), 5.33(1H,dd,J=6&10Hz), 8.42(1H,br), 9.92(1H,br)

Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
28		mp 137.5—139.5°C $C_7H_8BrFN_2O_4$ (283.07) Anal. C H N F cal. 29.70 2.85 9.90 6.71 F 29.79 2.86 9.62 6.81	IR(Nujol) 3400, 3100—3500, 1740, 1710 cm^{-1}	1.5—2.5(2H,m), 3.8—4.6(2H,m), 5.7(1H,S), 5.97(1H,m), 9.3—11.0(1H,br)
29		mp 167—169°C $C_8H_{11}FN_2O_3$ (202.188) Anal. C H N F cal. 47.52 5.48 13.86 9.40 F 47.17 5.33 13.76 9.31	IR(Nujol) 1750, 1720, 1700 cm^{-1}	2.30(2H,m), 3.3—4.1(2H,m), 4.8—5.4(3H,m), 5.5—6.2(2H,m), 8.03(1H,br), 9.87(1H,br)
30		$C_8H_{13}FN_2O_5$ (236.206)	IR(Nujol) 3100—3500, 1742, 1715, 1685 cm^{-1}	
31		mp 126—128°C $C_7H_9FN_2O_4$ (204.162) Anal. C H N F cal. 41.18 4.44 13.72 9.31 F 41.42 4.17 13.80 9.41	IR(Nujol) 3480, 1740, 1690 cm^{-1}	1.5—2.4(2H,m), 3.7—4.5(2H,m), 5.27(1H,dd,J=4&36Hz), 5.70(1H, dd,J=4&6Hz), 5.95(1H,m)
32		mp 152—155°C $C_{19}H_{38}BrFN_2O_4Si_2$(511.588) Anal. C H N F cal. 44.60 7.09 5.48 3.71 F 44.82 7.31 5.29 3.98	IR($CHCl_3$) 3380, 1760, 1710 cm^{-1}	0.03(6H,S), 0.22(6H,S), 0.90(9H,S), 0.98(9H,S), 1.4—2.4 (2H,m), 3.8—4.6(2H,m), 5.67 (1H,S), 6.07(1H,m)

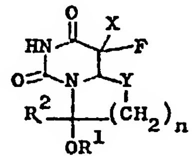
Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
33		mp 134—137°C $C_{13}H_{23}FN_2O_4Si$ (318.422) Anal. C H N F cal. 49.03 7.28 8.80 5.97 F 49.02 7.53 8.71 6.31	IR($CHCl_3$) 3380, 1750, 1710 cm^{-1}	0.17(6H,S), 0.95(9H,S), 1.4—2.0(2H,m), 3.7—4.7(2H,m), 5.18(1H,dd,J=4&29Hz), 5.58(1H,dd,J=4&12Hz), 5.92(1H,m)
34		mp 122—125°C $C_{13}H_{23}FN_2O_4Si$ (318.422) Anal. C H N F cal. 49.03 7.28 8.80 5.97 F 49.23 7.52 8.75 5.84	IR($CHCl_3$) 3380, 1755, 1710 cm^{-1}	0.10(3H,S), 0.17(3H,S), 0.90(9H,S), 1.5—2.0(2H,m), 3.8—4.4(2H,m), 4.95(1H,dd,J=7&30Hz), 5.45(1H,dd,J=7&9Hz), 5.95(1H,m)
35		mp 131—133°C $C_{13}H_{23}FN_2O_4Si$ (318.422) Anal. C H N F cal. 49.03 7.28 8.80 5.97 F 49.15 7.47 8.65 5.78	VV:λ_{max}^{EtOH}269mμ (ε=8,700) IR($CHCl_3$) 3390, 1705, 1675 cm^{-1}	0.08(3H,S), 0.20(3H,S), 0.92(9H,S), 1.8—2.2(2H,m), 3.67(2H,d,J=6Hz), 6.23(1H,dt,J=2&6Hz), 7.77(1H,d,J=6Hz)
36		mp 148—152°C $C_7H_9FN_2O_4$ (204.162) Anal. C H N F cal. 41.18 4.44 13.72 9.31 F 41.44 4.35 13.38 9.51	IR(Nujol) 3100—3500, 1760, 1732, 1715, 1690 cm^{-1}	1.6—2.1(2H,m), 3.8—4.4(2H,m), 4.97(1H,dd,J=8&30Hz), 5.45(1H,dd,J=8&9Hz), 5.85(1H,m)
37		mp 232—234°C $C_7H_9FN_2O_4$ (204.162) Anal. C H N F cal. 41.18 4.44 13.72 9.31 F 40.75 4.09 13.93 9.39	IR(Nujol) 3100—3500, 1765, 1750, 1715, 1682 cm^{-1}	1.7—2.2(2H,m), 3.8—4.2(2H,m), 4.97(1H,dd,J=8&30Hz), 5.47 (1H,dd,J=8&9Hz), 5.85(1H,m)

Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
38		mp 171—174°C $C_9H_{10}BrFN_2O_5$ (325.106) Anal. C H N F cal. 33.25 3.10 8.62 5.84 F 33.19 3.12 8.44 6.13	IR($CHCl_3$) 3380, 1760, 1710 cm^{-1}	1.83—2.57(2H,m), 2.17(1H,S), 4.1—5.6(2H,m), 5.70(1H,d,J=2Hz), 6.83(1H,m)
39		mp 150—154°C $C_9H_{11}FN_2O_5$ (246.198) Anal. C H N F cal. 43.91 4.50 11.38 7.72 F 44.15 4.48 11.35 7.95	IR(Nujol) 1760, 1730, 1710 cm^{-1}	2.03(3H,S), 1.7—2.3(2H,m), 3.9—4.3(2H,m), 5.03(1H,dd,J= 8&24Hz), 5.53(1H,dd,J=8&12Hz),, 6.77(1H,m)
40		mp 153.5—155.5°C $C_9H_{11}FN_2O_5$ (246.198) Anal. C H N F cal. 43.91 4.50 11.38 7.72 F 44.19 4.14 11.43 7.90	IR(Nujol) 1760, 1735 cm^{-1}	2.10(3H,S), 1.8—2.4(2H,m), 4.0—4.3(2H,m), 5.23(1H,dd,J= 4&32Hz), 5.67(1H,dd,=J=4&8Hz), 6.78(1H,m)
41		mp 107—110°C $C_{15}H_{22}BrFN_{22}O_5$ (409.262) Anal. C H N F cal. 44.02 5.42 6.85 4.64 F 44.14 5.45 6.70 4.58	IR($CHCl_3$) 3380, 1760, 1710 cm^{-1}	0.88(3Ht,J=5Hz), 1.1—2.4(2H and 10H,m), 2.50(2H,t,J=7Hz), 4.0—4.6(2H,m), 5.63(1H,d,J=2Hz), 6.83(1H,m)
42		mp 178—179.5°C $C_{12}H_{16}BrFn_2O_5$ (367.182) Anal. C H N F cal. 39.25 4.39 7.63 5.17 F 39.77 4.41 7.35 4.95	IR(Nujol) 1760, 1745, 1690 cm^{-1}	1.25(9H,S), 1.8—2.4(2H,m), 4.0—4.5(2H,m), 5.58(1H,d,J=2Hz), 6.80(1H,m)

Compound No.	Structural Formula	m.p., Molecular Formula	UV, IR Spectrum	NMR Spectrum (d_6-Acetone)
43		mp 163—166°C $C_{12}H_{17}FN_2O_5$ (288.276) Anal. C H N F cal. 49.99 5.95 9.72 6.59 F 49.78 5.85 9.58 6.67	IR(Nujol) 1760 1730, 1700 cm^{-1}	1.20(9H,S), 1.7—2.6(2H,m), 3.9—4.3(2H,m), 5.08(1H,dd,J=8&34Hz), 5.58(1H,dd,J=8&8.5 Hz), 6.77(1H,m)
44		mp 85—86°C $C_{15}H_{23}FN_2O_5$ (330.356) Anal. C H N F cal. 54.53 6.99 8.48 5.75 F 54.45 6.94 8.45 5.78	IR($CHCl_3$) 1740, 3380 cm^{-1}	0.87(3H,t,J=5Hz), 1.1—2.4(2H&10H,m), 2.37(2H,t,J=7Hz), 3.9—4.4(2H,m), 5.07(1H,dd,J=8&29.5Hz), 5.55(1H,dd,J=8&12Hz), 6.85(1H,m)
45		oil $C_{15}H_{23}FN_2O_5$ (330.356)	IR($CHCl_3$) 3380, 1750, 1710 cm^{-1}	0.88(3H,t,J=5Hz), 1.1—2.4(2H&10H,m), 2.42(2H,t,J=6Hz), 3.9—4.3(2H,m), 5.17(1H,dd,J=4&32Hz), 5.63(1H,dd,J=4&8Hz), 6.75(1H,m)

CLAIMS

1. A compound of the formula:



(I)

wherein R^1 is hydrogen, C_1—C_5 alkyl, C_6—C_{10} aryl, C_7—C_{10} aralkyl, C_1—C_{12} alkanoyl, C_2—C_6 alkoxycarbonyl, C_1—C_5 alkanoyloxymethyl, carbamoyl or tri-C_1—C_5 alkylsilyl; R^2 is hydrogen, C_1—C_5 alkyl, C_6—C_{10} aryl or C_7—C_{10} aralkyl;
X is hydrogen, halogen or C_2—C_6 alkoxycarbonyl;
Y is O, NR′ (R′ being hydrogen or C_1—C_5 alkyl), S, SO or SO_2; and
n is an integer of from 1—3.

2. dl- 8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-3α-trimethyl-acetoxy-5H-oxazolo[3,2-c]pyrimidine.

3. dl-8α-fluoro-2,3,6,7,8,8aα-hexahydro-3α-octanoyloxy-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine.

4. dl- 3α-acetoxy-8α-fluoro-2,3,6,7,8,8aα-hexahydro-5,7-dioxo-5H-oxazolo[3,2-c]pyrimidine.

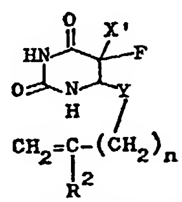
5. dl- 9α-fluoro-3,4,7,8,9,9aα-hexahydro-6,8-dioxo-4α-trimethyl-acetoxy-2H,6H-[1,3]-oxazino[3,2-c]pyrimidine.

6. A compound as claimed in claim 1 wherein R^1, R^2, X and/or Y is/are a group/groups referred to hereinbefore in exemplification of such groups.

7. A compound as claimed in claim 1 and referred to hereinbefore.

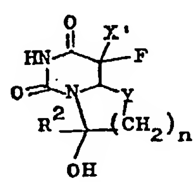
8. A compound as claimed in any one of claims 1 to 7 for use as an anti-tumour agent.

9. A process for preparing a compound as claimed in claim 1, which process comprises either:—
(a) subjecting a compound of the formula:



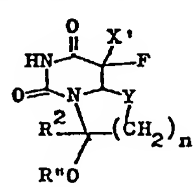
,

wherein X′ is halogen, to ozonolysis, optionally in the presence of methanol, to produce a compound of the formula:



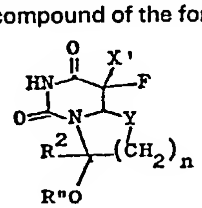
,

and, optionally acylating or alkylating the resulting compound to give compound of the formula:



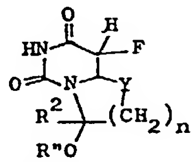
,

wherein R″ is the same as R^1 in formula (I) (claim 1) except for hydrogen; or
(b) reductively eliminating halogen X′ from a compound of the formula:



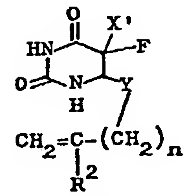
,

wherein R″ is as defined in (a) above and X′ is halogen, to produce a compound of the formula:



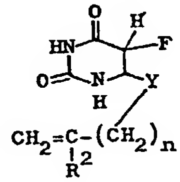
;

or (c) reductively eliminating hydrogen X′ from a compound of the formula:

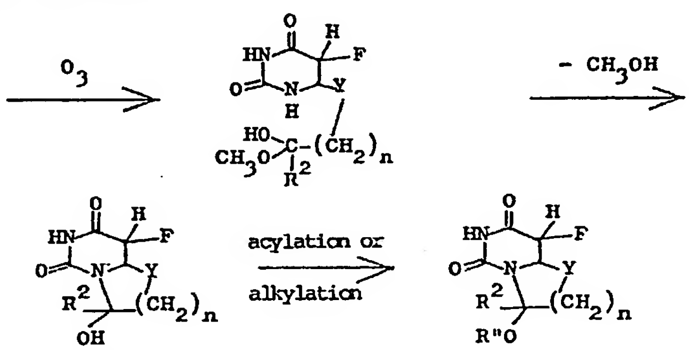


,

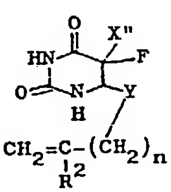
wherein X′ is halogen, and subjecting the resulting compound of the formula:



to the following reaction sequence:

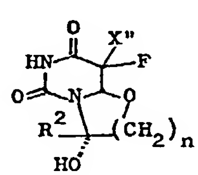


wherein R″ is as defined in (a) above; or
(d) subjecting a compound of the formula:

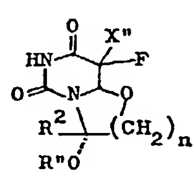


,

wherein X″ is C_2—C_6 alkoxycarbanyl, to a procedure analogous to that set out in (a) above to produce a compound of the formulae:



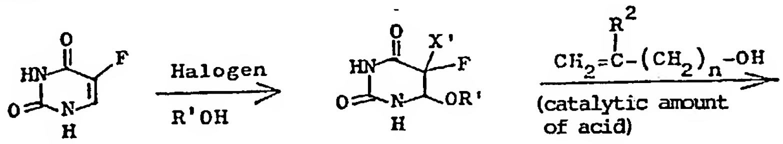
or



,

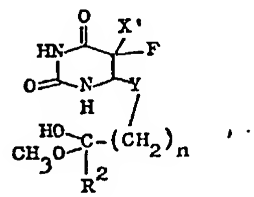
wherein R″ is as defined in (a) above.

10. A process as claimed in claim 9 (a), wherein Y is O and the starting compound has been produced in accordance with the following scheme from 5FU:



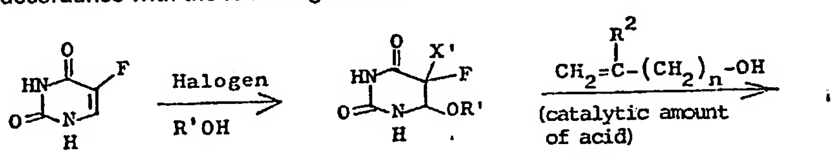
wherein R′ is hydrogen, lower alkyl or lower alkanoyl.

11. A process as claimed in claim 9 (a) or claim 10, wherein the ozonolysis of the starting compound is effected in the presence of methanol to produce a stable intermediate of the formula:



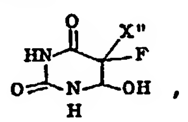
which is thereafter cyclized with elimination of methanol.

12. A process as claimed in claim 9 (c) wherein Y is O and the starting compound has been produced in accordance with the following scheme from 5FU:



wherein R′ is hydrogen, lower alkyl or lower alkanoyl.

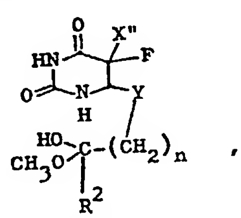
13. A process as claimed in claim 9 (d), wherein Y is O and the starting compound has been produced by reacting a compound of the formula:



with an unsaturated alcohol of the formula:

$$CH_2{=}\overset{\overset{\displaystyle R^2}{|}}{C}{-}(CH_2)_n{-}OH$$

14. A process as claimed in claim 9 (d) or claim 13, wherein the ozonolysis of the starting compound is effected in the presence of methanol to produce a stable intermediate of the formula:



which is thereafter cyclized with elimination of methanol.

15. A process for preparing a compound as claimed in claim 1 and substantially as hereinbefore described.

16. A process for preparing a compound as claimed in claim 1 and substantially as hereinbefore described in any one of the Examples.

17. A pharmaceutical or veterinary formulation comprising a compound as claimed in any one of claims 1 to 7 formulated for pharmaceutical or veterinary use, respectively.

18. A formulation as claimed in claim 17 and in unit dosage form.

19. A formulation as claimed in claim 17 or claim 18 also comprising a pharmaceutically acceptable or veterinarily acceptable, respectively, diluent, carrier or excipient.

20. A formulation as claimed in claim 17 and substantially as hereinbefore described.

21. A formulation as claimed in any one of claims 17 to 20 for use in producing an anti-tumour effect in an animal.

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